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Complement C1q subcomponent subunit A

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Complement C1q subcomponent subunit A (C1qA) is one of the three components of C1q molecule. Functional C1q is composed of eighteen polypeptide chains: six C1qA chains, six C1qB chains, and six C1qC chains, which are arranged as six heterotrimers of ABC: $(ABC)_6$. Each of the individual C1q polypeptide chain consists of a N-terminal region and a C-terminal globular region (gC1q), of ~135 residues. Each N-terminal consists of 2-11 amino acid segments containing a half-cysteine residue that is involved in formation of inter-chain disulphide bonds, followed by a collagen-like region (CLR) consisting of ~81 residues. The collagen-like regions in A, B and C chains of each heterotrimer come together to form a triple helical collagen like structure. Further, A and B chains in each heterotrimer are bound by a disulphide bond, while C chain forms a disulphide bond with a C chain from the adjoining heterotrimer. Therefore the eighteen subunits come together to form six globular heads (gC1q), which are clusters of 3 independently folded C-terminal domains of the A, B and C chain. These globular domains recognize an array of self, non-self and altered-self ligands. C1q associates with the proenzymes C1r and C1s (2 molecules of each, in the molar ratio of 1:2:2 in a calcium dependent manner) to yield an active C1 complex, the first component of the serum complement system. C1r, upon binding of gC1q to an inciting stimulus, autoactivates itself and catalyzes breakage of a C1s ester bond, resulting in C1s activation and subsequent cleavage of C2 and C4 into their respective "a" and "b" fragments. Recognition of ligands by C1q molecule also defines C1q as a pattern recognition molecule (PRM). C1q recognizes distinct structures either directly on microbial structures and apoptotic cells, or indirectly after their recognition by antibodies or C-reactive protein (CRP). C1q in turn binds to multiple receptors (such as cC1qR (calreticulin), integrin $\alpha_2\beta_1$ or other molecules on the surface of specific cell types of either myeloid or endothelial cell orgin) and shows regulated broad physiological functions beyond complement activation.

KEYWORDS
C1QA; Complement C1q subcomponent subunit A; Complement component 1, q subcomponent, A chain; Complement component 1, q subcomponent, alpha polypeptide; Complement component C1q, A chain

IDENTIFIERS
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PROTEIN FUNCTION
C1qA (C1qB and C1qC as well) has functions as part of the C1q or C1 complex. C1q complex is formed of six subunits each of C1qA, C1qB and C1qC. C1q in turn, associates with C1r and C1s to form the C1 enzyme complex ($C1qC1r_2C1s_2$).

Activation of classical complement pathway: Binding of C1q to immunoglobulins (Ig) or to other specific molecules generally associated with microbes, apoptotic cells or polyanionic structures such as DNA, activates C1q associated C1r and C1s, which are serine proteases. These proteases then cleave downstream complement proteins, C4 and C2, to result in C4a, C4b2a and C2b. C4b2a sequentially recruits and activates downstream complement proteins, while C4a and C2b can serve as anaphylotoxins.

Opsonization/phagocytosis: C1q interacts with immunoglobulin (IgG or IgM) bound targets, which could be either pathogens or host cells expressing altered self-ligands. Along with the C1q role in complement activation, C1q is also involved in clearance of apoptotic cells (Trouw *et al*. 2008). C1q can directly bind to some of the surface expressed macromolecules on apoptotic cells (such as DNA, lipids, newly exposed proteins) (Nauta *et al*. 2002; Navratil *et al*. 2001). C1q binding opsonizes the apoptotic cells and activates classical complement pathway (Zwart *et al*. 2004; Gaboriaud *et al*. 2011). Apoptotic cell clearance can be enhanced by C1q independent of the remaining complement components, but is further increased with classical pathway activation. Macrophages show reduced ability to take up apoptotic cells in individuals deficient in C1q, C4, C2 or C3 (Gullstrand *et al*. 2009). Apoptotic neuronal cells are also recognized by C1q, which again independently or engaging the other complement components (if present in the tissue) leads to opsonization, and facilitates receptor mediated phagocytosis by activated microglia (Fraser *et al*. 2010). Clearance of apoptotic cells requires interaction of C1q with its various receptors and has other effects on phagocyte cytokine production (see' Interaction with ligands and other proteins' section).

Mannose binding lectin 2 (MBL2), which activates the lectin pathway, is structurally similar to C1q and can therefore compete with C1q for binding to many altered self-ligands (Oroszlán *et al*. 2007; Agostinis *et al*. 2012). Both C1q and MBL2 enhance ingestion of modified low density lipoprotein (LDL) by monocytes and macrophages, and modulate monocyte activation and chemokine responses during the clearance of oxidized LDL (OxLDL) (cholesterol efflux) in OxLDL-loaded monocytes and macrophages (Fraser and Tenner 2010).

Inflammation: Complement activation that follows binding of C1q and cascade activation through cleavage of C5 leads to inflammation. However, inflammation is not always harmful, as it leads to host defense against pathogens and several other threats. For instance, C1q can bind to outer membrane proteins of Gram-negative bacteria and lead to complement susceptibility of the invading pathogen (Roumenina *et al*. 2008). On the other hand, C1q bound to "self-cargo" directly inhibits inflammasome activation, cleavage of caspase-1, and subsequent IL-1β processing in human monocyte derived

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macrophages (HMDMs) (Benoit *et al*. 2012). C1q bound to apoptotic lymphocytes increases the expression of nucleotide-binding domain and leucine-rich repeats protein 12 (NLRP12), an important inhibitor of inflammatory gene expression in human myeloid cells, and also increases the negative regulators of inflammasome activation such as POP1/ASC2 (a protein which modulates NF-κB activity) mRNA levels (Benoit *et al*. 2012).

Expression of cytokines and interleukins: Binding of C1q to immune cells generally results in suppression of pro-inflammatory cytokines and enhanced expression of anti-inflammatory cytokines. Interaction of C1q with human monocytes or dendritic cells results in the downregulation of proinflammatory cytokines upon toll-like receptor 4 (TLR4) stimulation by lipo-polysaccharide (LPS) (Fraser *et al*. 2006; Yamada *et al*. 2004). C1q bound apoptotic lymphocytes increase the expression of interleukin (IL)-33 which is a recently described member of the IL-1 family that can amplify M2 (alternative) polarization of macrophages induced by IL-13 (Benoit *et al*. 2012; Joshi *et al*. 2010). C1q bound apoptotic lymphocytes increase the expression of IL-37 (IL-IF7) which is a natural suppressor of innate inflammatory responses (Benoit *et al*. 2012; Nold *et al*. 2010). C1q sequentially induces type I interferons, IL-27, and IL-10 secretion in LPS-stimulated human macrophages (Fraser *et al*. 2009; Fraser *et al*. 2006; Benoit *et al*. 2012).

Immune cell maturation: C1q influences the maturation and function of dendritic cells (DCs) (Csomor *et al*. 2007; Castellano, et al, 2004; Baruah, et al, 2009). DCs cultured on immobilized C1q have a modulating effect on the T-cell production of interferon γ (IFNγ) and IL-17 in an mixed leukocyte reaction (MLR) reaction (Teh *et al*. 2011). Immature DCs are also good sources of C1q on their own (Csomor *et al*. 2007; Castellano *et al*. 2007), and additionally express the C1q receptors, gC1qR (gC1qBP, p33) and cC1qR (calreticulin). DCs have been reported to migrate in response to soluble C1q with maximal cell movement observed at 0.01-0.05μM C1q. In contrast, mature DCs neither express C1qR nor do move to a gradient of soluble C1q (Vegh *et al*. 2006). DC-SIGN (CD209), a transmembrane C-type lectin, which has been shown to interact with both C1q and gC1qR, probably plays a role in DC maturation (Hosszhu *et al*. 2012). C1q may also be involved in modulating T-cell and B-cell activity (Chen *et al*. 1994). C1q, by binding to platelets, modulates platelet aggregation, P-selectin production and thereby regulates platelet activation (Skoglund *et al*. 2010).

REGULATION OF ACTIVITY

Host cell factors: The modified apoptotic cell surface acquires C-reactive protein(CRP) and C1q together with factor H (fH) (Zipfel and Skerka 2009; Gershov *et al*. 2000) and C4b binding protein (C4BP) (Trouw *et al*. 2007). CRP, which is a pentraxin, promotes binding of C1q to the cell surface, while fH and C4BP prevent C3b deposition and amplification by the alternative pathway. The levels of CRP, fH and C1q shift the balance either towards complement activation or limited activation that may facilitate ingestion without downstream inflammatory anaphalatoxins or membranolytic complex formation. Other pentraxins, such as PTX3 and serum amyloid P-component, also activate C1 by binding to C1q ((Bottazzi *et al*. 1997; Nauta, et al, 2003) and reviewed in Bottazzi *et al*. 2010) and MBL can also play a role in targeting a pathogen for enhanced complement activation in conjunction with pentraxins and C1q in C1 (Ma *et al*. 2011). Inhibition of the C1 complex activity of can be useful in protecting against host cell damage. Formation of C1 complex can be inhibited by binding of C1q to surfactant associated protein A (SP-A) and chondroitin sulfate proteoglycan (CSPG4) (Watford *et al*. 2001; Kirschfink *et al*. 1997). C1q binding to IgG is inhibited by heme (Roumenina *et al*. 2011). Active C1q binds strongly to decorin and biglycan, which are leucine-rich proteoglycans involved in matrix assembly and bone mineralisation, respectively (Groeneveld *et al*. 2005). The binding of these extracellular matrix proteins hampers activation of complement cascade. Decorin and biglycan prevent C1q binding to human umbilical vein endothelial cells (HUVEC) and U937 cells, with biglycan further inhibiting C1q-mediated release of monocyte chemoattractant peptide-1 (MCP-1) and IL-8 from HUVEC (Groeneveld *et al*. 2005).

Pathogenic factors: The human astrovirus have special coat proteins that bind to C1q and inhibit the complement activation and hence evade the host immune response (Bonaparte *et al*. 2008; Hair *et al*. 2010). *Trypanosoma cruzi* calreticulin (TcCRT) prevents C1 complex formation, by interfering with the ability of the $(C1r–C1s)_2$ tetramer to bind C1q (Valck *et al*. 2010).

INTERACTIONS

C1qA chain binds to C1qB and C1qC chains to form a heterotrimer. Six such heterotrimers come together to form a functional C1q molecule (Kishore and Reid 2000). C1q has an N-terminal collagen-like region (CLR), also known as collagen stem or tail region, and C-terminal globular heads. The 3-dimensional crystal structure of the C1q globular domain has been solved (Gaboriand *et al*. 2003). Circulating C1q is bound in equilibrium with the tetramer of serine proteases $C1r_2C1s_2$, as C1 complex (Ziccardi and Tschopp 1982). This interaction with C1r and C1s occurs at the collagen-like region of the C1q molecule (Philips *et al*. 2009; Bally *et al*. 2009; Roumenina *et al*. 2011). C1s cleaves C4 to C4a and C4b. C4b recruits C2 which is then cleaved by the active C1 complex resulting in active products, C4b2a and C2b (Rossi *et al*. 1998).

Binding to ligands: The serine proteases C1r and C1s of C1 become activated when two or more gC1q domains of C1q bind to its ligands. One such ligand is the aggregated IgG or IgM immune complexes. This binding is ionic in nature and the B chain module of the gC1q in particular is implicated in facilitating the binding of C1q to IgG (Schneider and Zacharias 2012; Zlatorova *et al*. 2006; Gadjeva *et al*. 2008; Kojouharova *et al*. 2010). Pentraxins, such as PTX3 and serum amyloid P-component (SAP) can also bind C1q and facilitate activation of the complement cascade (Bottazzi et al. 1997; Bristow and Boackle 1986; Roumenina,et al 2006). PTX3, which also binds to C4 binding protein (C4BP) and fH, plays an important role in innate immunity (Doni et al. 2012; Cieślik and Hrycek 2012). PTX3 has been shown to form a tri-complex with C1q and MBL on the surface of *Candida albicans* (Ma *et al*. 2011). Binding of C1q to β amyloid protein in β sheet fibrils (Rogers *et al*. 1992; Jiang *et al*. 1994; Tacnet-Delorme *et al*. 2001) and to prion proteins activates the complement cascade and thereby promotes inflammation of the tissue (Blanquet-Grossard *et al*. 2005; Dumestre-Pérard *et al*. 2007). Binding of C1q *via* the head region to short leucine-rich glycoproteins (SLRPs) such as osteoadherin and fibromodulin can activate the complement cascade (Sjöberg *et al*. 2009). However, SLRPs such as decorin and biglycan, which bind to the collagen-like region, downregulate activity (Sjöberg *et al*. 2009; Groeneveld et al. 2005). The classical complement pathway is also activated in

vascular injury which leads to inflammation. C1q interacts with platelets *via* gC1qR (gC1qBP, p33) binding the globular head of C1q (Ghebrehiwet *et al*.1994; Ghebrehiwet *et al*. 2001). Adaptor molecules, such as C-reactive protein (CRP), a pentraxin, play a major role in augmenting the binding capacity of C1q to platelets (Peerschke *et al*. 2006; Peerschke *et al*. 2009).

It is the C1q globular domain that binds the apoptotic cell surface (Korb and Ahearn 1997; Navratil et al. 2007). C1q can enhance apoptotic cell phagocytosis in cooperation with other surface receptors such as CR1, FcR, CD91 (reviewed in Bohlson *et al*. 2007) and most recently RAGE, the multi-ligand receptor of Ig super family, (Ma *et al*. 2012). For example, C1q demonstrates more efficient phagocytosis in the presence of both RAGE and integrin $\alpha_M\beta_2$ (CD11b/CD18), as compared to the individual presence of either of these proteins (Ma *et al*. 2012). CRP can also promote the binding of C1q to apoptotic cells, amplifying classical pathway activation while also recruiting fH, which inhibits alternative pathway amplification and C5 convertase formation, thereby protecting cells from necrotic lysis and the host from unwarranted inflammation (Gershov *et al*. 2000). Apoptotic cell surfaces expose ligands such as DNA, histones and amino groups of phospholipids. While C1q can directly bind to DNA and histones, there is currently a controversy as to whether C1q binds directly to phosphatidyl serine on apoptotic cells (Paidassi *et al*. 2008) or indirectly binds to phosphatidyl residues *via* annexins 2 and 5 or both, thus contributing to clearance by macrophages (Jiang *et al*. 1992, Martin *et al*. 2012).

C1q (or C1 complex) binds directly to a variety of altered-self ligands via gC1q domain (Gaboriaud *et al*. 2011). It can bind to oxidized and enzymatically modified forms of LDL (E-LDL) (Biró *et al*. 2007; Fraser and Tenner 2010), by recognizing unesterified cholesterol formed by cholesterol esterase (Biro *et al*. 2010). C1q can also bind to adiponectin (produced by adipose tissues) and when C1q is in the C1 complex activates the complement cascade (Peake *et al*. 2008; Nakatsuji *et al*. 2012). However, the binding is substantially increased by modification of adiponectin by metaperiodate, and thus the physiological role of this interaction remains to be determined. In rheumatoid arthritis condition, binding of C1q to histidine rich glycoprotein (HRG) aids in clearance of necrotic cells (Manderson *et al*. 2009). C1q has been reported to bind to decidual extracellular matrix, and may play a role in promoting trophoblast invasion of decidua (Agostinis *et al*. 2010).

C1q interacts with salivary scavenger and agglutinin (SALSA), which in turn binds to pathogens, leading to complement activation (Reichhardt *et al*. 2012; Boackle *et al*. 1993). Ligands from pathogenic microbes include Lipid-A of *E.coli* (Tan *et al*. 2011) and *Klebsiella pneumoniae* porin (OmpK36), both of which activate complement cascade and lead to destruction of the pathogen (Alberti *et al*. 1995; Alberti *et al*. 1996). C1q can bind to *Human immunodeficiency virus* (HIV) envelope proteins gp120 and gp41. In most cases, binding of gp120 and gp41 to C1q facilitates entry of the virus into CD4+ cells *via* complement receptors for C3 (Stoiber *et al*. 1994; Prohászka *et al*. 1995; Thielens *et al*. 2002; Stoiber *et al*. 1995; Ebenbichler *et al*. 1991; Thieblemont *et al*. 1993a; Thieblemont *et al*. 1993b). In one report, binding of gp120 to C1q, in presence of fibronectin reduced infection in saliva (Su and Boackle 1991). In dendritic cells, C1q-gC1qR forms a tri-molecular complex with DC-SIGN, a C-type lectin (Hosszu *et al*. 2012).

Binding to the receptors on host immune cells *via* collagen-like stem region (CLR):

CLR domain of C1q enhances phagocytosis of suboptimally opsonized immune complexes as well as apoptotic cells and cell debris. However, the cell surface receptors involved have not been definitively established, and likely involve complexes of surface molecules. cC1qR (Calreticulin or CRT) is a well-studied and most ubiquitous C1q receptor thought to be involved in mediating C1q effects on biological processes (Malhotra *et al*. 1990; Malhotra 1993; Nicholson-Weller and Klickstein 1999). It is produced intracellularly, but is exposed on the cell surface of damaged cells. This protein facilitates binding of C1q to a receptor CD91(LRP1,A2MR), and was thereby proposed to promote phagocytosis of apoptotic cells (Ogden *et al*. 2001). In addition, a recent study has supported evidence for the possibility of CD91 directly recognizing C1q (Duus *et al*. 2010). However, genetic abrogation of the CD91 expression in mice did not reduce the C1q enhancement of uptake (Lillis *et al*. 2008), suggesting redundancy of receptors or compensary mechanisms. CR1(CD35), yet another cell surface C1q binding molecule, also binds to other opsonins (C3b and C4b). This interaction favors cell adhesion and thereby apoptotic cell clearance (Tas et al. 1999; Klickstein *et al*. 1997). CD93, a protein expressed on myeloid lineage cells, endothelial cells, and platelets was originally considered the C1qR that mediated enhanced phagocytic activity (C1qRP)(Nepomuceno *et al*. 1997; Nepomuceno and Tenner, 1998; Fonseca *et al*. 2001) but genetic abrogation had no effect on *in vitro* C1q enhanced phagocytosis and thus is not necessary for this C1q function (similar to CD91). Its roles include angiogenic properties and involvement in endothelial cell migration and intercellular adhesion (Greenlee *et al*. 2008; Bohlson *et al*. 2007). The α2β1 integrin has also shown the ability to function as a C1q receptor (Edelson *et al*. 2006). This integrin is expressed on a variety of cell types including mast cells, and has been reported to bind to C1q, implying a role for this integrin in innate immunity (Zutter and Edelson 2007), but also as a C1q dependent mechanism for bacteria invasion (Xue *et al*. 2011). Interestingly, *Trypanosoma cruzi* calreticulin (TcCRT) binds to C1q and prevents C1 formation, by interfering with the ability of the $(C1r–C1s)_2$ tetramer to bind C1q (Valck *et al*. 2010). Fibrinogen, a protein composed of α, β and γ chains, binds to C1q and may also facilitate phagocytosis (Entwistle and Furcht 1988).

PHENOTYPES

The A, B, and C chains of C1q are arranged in the order A-C-B on human chromosome 1 and are transcribed in a synchronized manner (Chen *et al*. 2011). An insertion polymorphism has been identified in the murine New Zealand Black (NZB) C1q gene that correlated with lower C1q levels in sera and production by macrophages *in vitro* (Miura-Shimura *et al*. 2002). While little more is known of the transcriptional control of C1q, some analysis of the gene locus has been provided (Lattin *et al*. 2009), with evidence that a deficiency in β-arrestin 2 abrogates C1q synthesis in murine bone marrow dervied macrophages (Lattin *et al*. 2009).

C1qA alleles showing single nucleotide polymorphisms (SNP) have been documented (Racila *et al*. 2003; Namjou *et al*. 2009; Cao *et al*. 2012). There are two forms of C1q deficiency. One

form produces no C1q, and the other form produces a dysfunctional C1q (includes non-sense and mis-sense mutations) (Kirschfink *et al*. 1993; Petry *et al*. 1997; Hoekzema *et al*. 1985). Genetic analysis of the C1q-deficient patients has revealed mutations affecting each of its three chains (Petry *et al*. 1995; Mayilyan 2012; Namjou *et al*. 2012; Topaloglu *et al*. 2012). C1q deficiency, a rare autosomal recessive disorder, is known to result in an increased risk for bacterial infections, recurrent skin lesions, chronic infections, and autoimmune diseases such as, systemic lupus erythematosus (SLE) or SLE-like diseases and lupus nephritis (Petry 1998; Bowness *et al*. 1994; Carroll 1998; Tsao 1998; Stone *et al*. 2000; Pickering *et al*. 2000). Recent studies have shown SLE patients, with or without lupus nephritis, to express anti-C1q antibodies (Jourde-Chiche *et al*. 2012; Katsumata *et al*. 2011; Yin *et al*. 2012). Epitopes for anti-C1q antibodies in lupus nephritis patients have been reported (Vanhecke *et al*. 2012; Stoyanova *et al*. 2012). In patients with C1q deficiency, serum and cerebrospinal fluid levels of IFN-α and IFN-γ-inducible protein-10 levels were elevated and strongly correlated with Ro autoantibodies (Santer *et al*. 2010). A C1q homozygous mutation at GlyB63Ser, resulting in lupus condition, exhibits a normal C1q structure, and can bind to immunoglobulins and pentraxins. However, this mutation abrogates binding of C1r, implying that mere ligand recognition is not enough to prevent lupus condition (Roumenina *et al*. 2011) and/or this site may be involved with C1q interaction with and signaling of host cells to enhance uptake of apoptotic cells and suppress production of inflammatory mediators.

MAJOR SITES OF EXPRESSION

C1q is predominantly synthesized by peripheral tissue macrophages and dendritic cells *in vivo* (Petry *et al*. 1991; Castellano *et al*. 2010) and by macrophages, microglia and dendritic cells *in vitro* (Tenner and Volkin 1986; Castellano *et al*. 2004; Bensa *et al*. 1983). This local myeloid cell synthesis of C1q is hypothesized to be the major source of C1q for the rapid opsonization of dying cells in tissue, before recruitment of plasma-derived components such as C1r and C1s and subsequent activation of the complement cascade (Benoit *et al*. 2012). Induced synthesis of C1q has been detected in several injury models *in vivo* and *in vitro*, including in atherosclerotic lesions (Cao *et al*. 2003), suggesting that the induction of C1q synthesis in tissue may be a response to injury that promotes rapid clearance of apoptotic cells and concomitant suppression of inflammation (Dietzschold *et al*. 1995). A recent report has shown osteoclasts to produce C1q, which in turn leads to osteoclast development (Teo *et al*. 2012). Neurons can also be induced to produce C1q by injury or infection or during development (reviewed in Alexander *et al*. 2008).

SPLICE VARIANTS

There are no known splice variants.

REGULATION OF CONCENTRATION

A recent method has estimated C1q concentration to be ~113 +/- 40 µg/ml in normal serum. However, previous studies have shown concentrations to range from 56 - 276 µg/ml (Ziccardi and Cooper 1978; Dillon *et al*. 2009). Ratio of C1q bound adiponectin to total adiponectin in blood has been reported to serve as a biomarker for cardiovascular risk (Nakatsuji *et al*. 2012).

ANTIBODIES

C1q monoclonal antibodies (mAbs) can be obtained from Quidel Corporation. This monoclonal antibody, raised against purified human C1q protein, is specific for the globular head domain (Stoltzner *et al*. 2000). Several monoclonal antibodies to human C1q were produced and characterized as to reactivity with the globular domain *vs* collagen like region by Kilchherr and colleagues (Kilchherr *et al*. 1985).

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
C1QA	extracellular region	
C1qA/C1qB/C1qC	extracellular region	Kishore U and Reid KB 2000
C1q	extracellular region	Kishore U and Reid KB 2000
C1q/CRP	extracellular region	Volanakis JE and Narkates AJ 1981
C1q/PTX3	extracellular region	Bottazzi B *et al.* 1997
C1q/SAP	extracellular region	Bristow CL and Boackle RJ 1986
C1q/PrP	extracellular region	Blanquet-Grossard F *et al.* 2005; Dumestre-Pérard C *et al.* 2007; Hasegawa M *et al.* ; Jiang H *et al.* 1994; Mitchell DA *et al.* 2007; Sjöberg AP *et al.* 2008; Snyder SW *et al.* 1994; Sørensen IJ *et al.* 1996; Tacnet-Delorme P *et al.* 2001; Webster S *et al.* 1997; Webster S *et al.* 1995; Ying SC *et al.* 1993
C1q/Fibrinogen	extracellular region	Binnie CG and Lord ST 1993; Entwistle RA and Furcht LT 1988; Guan EN *et al.* 1991; Mosesson MW *et al.*
C1q/Fibrin	extracellular region	Entwistle RA and Furcht LT 1988
C1q/Adiponectin	extracellular region	Nakatsuji H *et al.* 2013; Peake PW *et al.* 2008
C1q/[Decorin/Biglycan]	extracellular region	Krumdieck R *et al.* 1992; Groeneveld TW *et al.* 2005; Sjöberg AP *et al.* 2009
C1q/α2β1	plasma membrane	Edelson BT *et al.* 2006
C1q/C1qR	plasma membrane	Malhotra R and Sim RB 1989; Malhotra R *et al.* 1990; Arvieux J *et al.* 1984
C1q/gC1qR	extracellular region	Ghebrehiwet B *et al.* 2001; Ghebrehiwet B *et al.* 1994
C1q/gC1qR/DC-SIGN	plasma membrane	Hosszu KK *et al.* 2012
C1q/cC1qR	extracellular region	Csomor E *et al.* 2007; Nicholson-Weller A and Klickstein LB 1999; Ogden CA *et al.* 2001; Stuart GR *et al.* 1997
C1q/CD91	plasma membrane	Duus K *et al.* 2010
C1q/cC1qR/CD91	plasma membrane	Ogden CA *et al.* 2001
C1q/CR1	plasma membrane	Tas SW *et al.* 1999; Klickstein LB *et al.* 1997
C1q/IgG	extracellular region	Emanuel EJ *et al.* 1982; Gadjeva MG *et al.* 2008; Hughes-Jones NC and Gardner B 1979; Hughes-Jones NC and Gardner B 1978; Kaul M and Loos M 1997; Kojouharova MS *et al.* 2004; Mårtensson U *et al.* 1992; Vandenberg RJ and Easterbrook-Smith SB 1986; Zlatarova AS *et al.* 2006; Duncan AR and Winter G 1988
C1q/IgM	extracellular region	Gadjeva MG *et al.* 2008; MacKenzie MR *et al.* 1971; Poon PH *et al.* 1985; Poon PH and Schumaker VN 1991; Weiner EM *et al.* 1988; Zlatarova AS *et al.* 2006
C1q/APOA1	extracellular region	Zhou M *et al.* 2004
C1q/DC-SIGN	plasma membrane	Hosszu KK *et al.* 2012
C1q/CSPG4	extracellular matrix	Kirschfink M *et al.* 1997
C1q/SP-A	extracellular region	Watford WT *et al.* 2001
C1q/LDL	extracellular region	Biró A *et al.* 2007; Fraser DA and Tenner AJ 2010
C1q-DNA	extracellular region	Jiang H *et al.* 1992
C1q/RAGE	extracellular region	Ma W *et al.*
C1q/αMβ2	plasma membrane	Ma W *et al.*
C1q/αMβ2/RAGE	plasma membrane	Ma W *et al.*
C1q/SALSA	extracellular region	Boackle RJ *et al.* 1993; Reichhardt MP *et al.*
C1q/HRG	extracellular matrix	Manderson GA *et al.* 2009
C1q/SLRP	extracellular matrix	Sjöberg AP *et al.* 2009
C1q/β-Amyloid	extracellular region	Jiang H *et al.* 1994; Rogers J *et al.* Jul-Aug; Tacnet-Delorme P *et al.* 2001
C1q/Histone[3,4]	extracellular region	Martin M *et al.* 2012
C1q/Histone2[a,b]/Histone1	extracellular region	Martin M *et al.* 2012
C1q/Annexin[2,5]	extracellular region	Martin M *et al.* 2012
C1q/OmpK36 (K. pneumoniae)	extracellular region	Albertí S *et al.* 1995; Albertí S *et al.* 1996
C1q/FKBP2	Unknown	Neye H and Verspohl EJ 2004
C1q/HIV-gp120 (HIV)	extracellular region	Prohászka Z *et al.* 1995; Su H and Boackle RJ 1991; Thielens NM *et al.* 2002; Stoiber H *et al.* 1994
C1q/HIV-gp41 (HIV)	extracellular region	Ebenbichler CF *et al.* 1991; Stoiber H *et al.* 1995
C1q-Lipid A (E. coli)	extracellular region	Tan LA *et al.* 2011
C1q/TcCRT (T. cruzi)	extracellular region	Valck C *et al.* 2010
C1q/Heme	extracellular region	Roumenina LT *et al.* 2011
C1qr2s2 (C1)	extracellular region	Gaboriaud C *et al.* 2004; Weiss V *et al.* 1986
C1/C4b	extracellular region	Rossi V *et al.* 1998

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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 46 states , has 47 transitions between these states and has 2 enzyme functions.(Please zoom in the pdf file to view details.)